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Tomatoes, Lycopene, and Risk of Prostate Cancer

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Abstract

Like other carotenoids, lycopene can protect plants from photo-oxidation damage, but its role in humans is unclear. In the United States, tomatoes provide 85–90% of dietary lycopene, with two-thirds contributed by tomato products. Tomatoes are also rich in vitamins C and A, folate, potassium, and several non-nutrient phytochemicals. Increased lycopene and tomato intake has been hypothesized to decrease the risk of prostate cancer, the most commonly diagnosed cancer among U.S. men. Of the 15 epidemiologic studies – 3 prospective and 12 retrospective – to evaluate this relationship, approximately half reported reductions in risk with increased intake (relative risks ~0.6–0.8 between extremes of intake). Protective effects were most consistently seen with cooked tomato products, possibly because of enhanced lycopene bioavailability, and in U.S. white men. The three prospective studies of prediagnostic blood lycopene levels, a biomarker which integrates intake, absorption, and metabolism, and prostate cancer have also not concurred. However, they do suggest that risk may be reduced (relative risks ~0.5–0.8) in U.S. white men, possibly because of relatively high circulating lycopene or linked dietary patterns and lifestyles. Thus, at present, epidemiologic research does not persuasively support or refute the protective promise of lycopene and tomatoes. Future research should focus on dietary and lifestyle determinants of blood lycopene levels, improved assessment of tomato product intake and incorporation of updated lycopene databases, direct measurement of lycopene in prostate tissue, and development of reliable intermediate markers of prostate carcinogenesis.

Keywords: Carotenoids, chemoprevention, epidemiology, lycopene, prostate cancer, tomatoes.

Prostate cancer is the most commonly diagnosed cancer among men living in the United States, and the second leading cause of cancer mortality (Ries et al., 2000). In 2000, approximately 180,000 men were diagnosed with this disease, and about 32,000 men died as a result (American Cancer Society, 2001). Worldwide, prostate cancer is the fourth most commonly diagnosed cancer among men, and the sixth cause of cancer mortality (Pisani et al., 1999). In 1990, age-standardized incidence rates were five-times higher in developed countries than in developing countries (Parkin et al., 1999), and varied by more than 50-fold among individual countries (Parkin et al., 1997).

The risk of prostate cancer increases with advancing age and a positive family history of prostate cancer (Clinton & Giovannucci, 1998). Race is also an important determinant; throughout the U.S., rates are consistently highest in Blacks, intermediate in Whites, lower in Hispanics, and lowest in Asians and American Indians (Parkin et al., 1997). Otherwise, the etiology of prostate cancer remains elusive. The international variation in incidence suggests that lifestyle and/or environment may be critical. Furthermore, temporal trends in many countries (Zaridze et al., 1984) and rates in migrant populations that approach those of the adopted country (Haenszel & Kurihara, 1968) portend that the risk factors can be modified. Several promising hypotheses implicate diet. Although the evidence is not conclusive, intake of red meat, dairy products, animal fat, saturated fat, and calcium have been postulated to increase risk, while vegetables, legumes, vitamins D and E, selenium, and lycopene have been postulated to reduce risk (Kolonel, 1996; Clinton & Giovannucci, 1998; Cohen et al., 2000; Kolonel et al., 2000). In this paper, we review the evidence for lycopene.

Lycopene is a carotenoid, a class of fat-soluble phytochemical that protect plants from photo-oxidation damage. *In vitro*, lycopene can be a potent antioxidant, with a singlet oxygen-quenching ability twice as high as β-carotene and 10-times as high as α-tocopherol (DiMascio et al., 1989).

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However, the role of lycopene in humans is not clear; unlike other carotenoids, such as β-carotene or α-carotene, lycopene cannot be converted to vitamin A.

In the United States, the major source of lycopene is tomatoes and tomato products. Based on a 1986 USDA survey, only 25–30% of the lycopene intake of young and middle-aged U.S. women comes from tomatoes and tomato juice (Chug-Ahuja et al., 1993). An additional 60% is provided by processed tomato products: tomato sauce, ketchup, pasta sauce, pizza, and soup. Although pink grapefruit, guava, and watermelon are as rich in lycopene as raw tomatoes (Mangels et al., 1993), they contribute only about 10% of dietary lycopene because of infrequent consumption. The absorption and bioavailability of lycopene are substantially enhanced by heat-processing and concurrent consumption of fat (Parker, 1996).

In blood samples from U.S. subjects, lycopene concentrations are generally the highest among the individual carotenoids. In a large, multicenter U.S. cohort of female nurses, another large, multicenter U.S. cohort of male physicians, and in the Third U.S. Health and Nutrition Examination Survey, lycopene, followed by β-carotene or lutein, was the carotenoid at the highest concentration in serum (Michaud et al., 1998; Wei et al., 2001). However, in older adults, >60 years, circulating lycopene levels are lower than those of β-carotene and lutein (Dixon et al., 2001). Recent research has suggested that although lycopene is present in prostate tissue, it may not be preferentially concentrated there, relative to other carotenoids (Freeman et al., 2000). The relative amounts of individual carotenoids in prostate tissue matched their proportions in plasma. Furthermore, in 47 men, lycopene levels in prostate tissue were moderately correlated with plasma levels (correlation coefficient [r] = 0.56), a finding that suggests that plasma lycopene might be a reasonable biomarker in epidemiologic studies. Conversely, dietary intake of lycopene, assessed with a detailed food frequency questionnaire, was only modestly correlated with plasma lycopene levels (r = 0.16) and essentially unable to predict tissue levels (r = –0.06) (Freeman et al., 2000).

Although tomatoes are often viewed as the single major source of lycopene in the diet, they are a complex mixture of nutrients and non-nutrient phytochemicals. Because tomatoes and tomato products rank second among all vegetables consumed in the U.S., they provide substantial quantities of many of these compounds (Beecher, 1998). In the American diet, tomatoes and tomato juice are the third highest contributor of vitamin C, the fourth highest contributor of vitamin A, and a major source of folate and potassium. Of the phytochemicals postulated to be related to cancer prevention, tomatoes are especially rich in the carotenoids: lycopene is the most abundant, followed by γ-carotene and phytoene, then β-carotene. Tomatoes also contain modest amounts of vitamin E and the flavonoid quercetin. Since the bioactive constituents in tomatoes have not yet been identified, it is not clear how to quantify tomato intake, or account for the impact of processing, in epidemiologic studies. Intake could be measured as servings or grams of tomato product; alternatively, lycopene might be the best metric for tomato intake.

Approximately 15 published studies have addressed the relationship between prostate cancer risk and dietary intake of tomatoes, tomato products, and/or lycopene (Table 1). In early work, protective effects (relative risks [RRs] ~ 0.6–0.7) were noted for increased tomato consumption in a case-control study in Minnesota (Schuman et al., 1982) and a cohort study in California Seventh Day Adventists (Mills et al., 1989), but not in a multiethnic case-control study in Hawaii (Le Marchand et al., 1991). In 1995, Giovannucci and collaborators highlighted the reduction in prostate cancer risk associated with both tomato product consumption and lycopene intake in a large, multicenter cohort of health professionals. In this cohort of 47,894 men, aged 40–75 at baseline, dietary intake for a one-year period was assessed with a mailed, semi-quantitative food frequency questionnaire that included 131 food items. This questionnaire had been calibrated against two one-week dietary records in 121 volunteers. During six years of followup, 773 incident cases of prostate cancer were documented. Of the five major carotenoids, only lycopene intake was associated with reduced risk (RR = 0.79, 95% confidence interval [CI] = 0.64 – 0.99, for high versus low quintile of intake); an inverse trend was apparent and statistically significant (Table 2). Of 46 vegetables, fruits, and related food items, only four were significantly associated with lower prostate cancer risk (Table 3). Of the four, tomato sauce, tomatoes, and pizza, but not strawberries, are important sources of lycopene. Stronger inverse gradients were seen with tomatoes and with tomato sauce than with lycopene. Combined intake of tomatoes, tomato sauce, tomato juice, and pizza, which together accounted for 82% of lycopene intake, was associated with a 35% reduction in risk of prostate cancer (RR = 0.65, 95% CI = 0.44 – 0.95, for >10 servings/week versus <1.5 servings/week; p for trend = .01), and an even greater reduction in risk, ~50%, of advanced disease.

These provocative, promising results rekindled the excitement about the protective potential of carotenoids, particularly lycopene, and were widely quoted. They emerged at a time when interest in the carotenoids was fading, primarily because of the failure of supplemental β-carotene to reduce lung cancer or total cancer incidence in three randomized, placebo-controlled clinical trials (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Hennekens et al., 1996; Omenn et al., 1996). However, in another cohort study, including 58,279 men aged 55–69 years at baseline and living in the Netherlands, neither tomatoes (RR = 1.05 for a 25 g/day increase, equivalent to a serving/week) nor tomato juice (RR = 1.12 for a 25 g/day increase) were associated with decreased prostate cancer risk (Schuurman et al., 1998). The design for this study was comparable to that of the Giovannucci et al. (1995) study. Intake of 150 food items over the past year was assessed with a mailed, semi-quantitative food frequency questionnaire,

Table 1. Summary of epidemiologic studies examining the relationship between dietary intake of tomatoes, tomato products, and/or lycopene and risk of prostate cancer.[a]

		Cases		Exposure assessment					
Authors	Study population	No.	% advanced disease[b]	Timing	Dietary variable(s)	Exposure range	OR or RR (**Bold** = $p < 0.05$)	p for trend	Controlled factors
Schuman et al., 1982	Minnesota, USA Hospital-based)	223	NK	Retro	Tomatoes	14+ vs. <3 servings/mo	0.71	NK	Age, date of hospital admission
Mills et al., 1989	California, USA (7th Day Adventists)	180	<50%	Prosp	Tomatoes	5+ vs. <1 servings/wk	**0.60**	NK	Age; education; intake of: meat, poultry, or fish; beans; legumes or peas; citrus fruit; dry fruit; index of fruit, nuts, tomatoes
LeMarchand et al., 1991	Hawaii, USA (Japanese, White Filipino, Chinese, Hawaiian)	452	NK	Retro	Tomatoes	High vs. low quartiles	<70 years: 0.9 70+ years: 1.1	0.35 0.57	Age, ethnicity
Giovannucci et al., 1995	USA (Health professionals)	773	35%	Prosp	Lycopene	>6460 vs. <2262 µg/day	**0.79**	**0.04**	Age; ancestry; vasectomy; intake of animal fat, retinol, energy
					Tomato-based products	10+ vs. <1.5 servings/wk	**0.65** Advanced cases: **0.47**	**0.01** **0.03**	
Key et al., 1997	England	328	29%	Retro	Lycopene	718+ vs. <402 µg/day	0.99	0.88	Age, social class
					Raw tomatoes	5+/wk vs. ≤3/mo	1.06	0.88	
					Cooked tomatoes	2+/wk vs. <1/mo	0.92	0.64	
Schuurman et al., 1998	Netherlands	610	NK	Prosp	Tomatoes	per 25 g/day increase	1.05	NK	Age, family history of prostate cancer, socioeconomic status, total fruit and vegetable consumption
					Tomato juice	per 25 g/day increase	1.12	NK	
Tzonou et al., 1999	Greece (Hospital-based)	320	6%	Retro	Raw tomatoes	Increasing quintiles	Inverse	0.12	Age, education, date of interview, hospital, height, Quetelet's index, energy
					Cooked tomatoes	Increasing quintiles	**Inverse**	**0.005**	

Table 1. Continued

Authors	Study population	Cases		Exposure assessment		Exposure range	OR or RR (**Bold** = $p < 0.05$)	p for trend	Controlled factors
		No.	% advanced disease[b]	Timing	Dietary variable(s)				
Jain et al., 1999	Canada	617	NK	Retro	Lycopene	>12,681 vs. <2103 µg/day	1.01	NK	Matched on age and residence; stepwise regression with: body mass index, education, marital status, vasectomy, smoking status, multivitamin use, grains, fruit, vegetables, total plants, total carotenoids, folic acid, dietary fiber, conjugated linoleic acid, vitamin E, vitamin C, retinol, total fat, linoleic acid, energy
					Tomatoes	>109.6 vs. <9.3 g/day	**0.64**	NK	
Villeneuve et al., 1999	Canada	1623	NK	Retro	Tomatoes or tomato juice	7+ vs. <1/wk	1.0	0.29	Age; race; province of residence; family history of cancer; income; years since quitting smoking, cigarette pack-years; body mass index; intake of rice and pasta, coffee, grains and cereals, alcohol, fruits and fruit juices, tofu, meat
Deneo-Pellegrini et al., 1999	Uruguay (Hospital-based)	175	70%	Retro	Lycopene	3301+ vs. ≤1300 µg/day	1.2	0.90	Age, residence, family history of prostate cancer, education, urban/rural, body mass index, energy

Hayes et al., 1999	USA (Black, White)	932	31%	Retro	Lycopene	5+ vs. 0 servings/wk	0.9 Advanced cases: 1.0	0.07 0.13	Age, study site, race, energy
					Cooked tomatoes and sauces	5+ vs. 0 servings/wk	1.0 Advanced cases: 1.6	0.71 0.95	
					Raw tomatoes	5+ vs. 0 servings/wk	0.8 Advanced cases: **0.5**	0.16 **0.04**	
Cohen et al., 2000	Washington, USA	628	26%	Retro	Lycopene	9900 + vs, <4900 µg/day	0.89	0.13	Age, race, family history of prostate cancer, education, prostate-specific antigen within the previous 5 years, body mass index
					Cooked tomatoes	3+ vs. <1 servings/wk	0.73	0.13	
					Raw tomatoes	3+ vs. <1 servings/wk	0.93	0.76	
Norrish et al., 2000	New Zealand	317	61%	Retro	Lycopene	>1994 vs. <662 µg/day	0.76	0.30	Age, socioeconomic status, height, total nonsteroidal anti-inflammatory drugs use
					Tomatoes and tomato-based foods	>64 vs. <19 g/day	0.82	0.30	
					Raw tomatoes	>35 vs. <13 g/day	1.01	0.93	
Kolonel et al., 2000	USA & Canada (Black, White, Japanese, Chinese)	1619	32%	Retro	Tomatoes	>108 vs. ≤20 g/day	1.07 Advanced only: 1.08	0.85 0.78	Age, ethnicity, region of residence, education, energy
					Cooked tomatoes	>93 vs. ≤18 g/day	0.94 Advanced only: 0.96	0.56 0.76	
Lu et al., 2001	USA (Hospital-based)	65	NK	Retro	Lycopene	>3450 vs. <1458 µg/day	0.69	0.47	Age, race, family history of prostate cancer, education, pack-years of smoking, energy

[a] "NK" = "not known"; "mo" = "month"; wk = "week".

[b] "Advanced" disease is defined variously by researchers. Therefore, one specific definition could not be provided.

Table 2. Relative risks[a] of prostate cancer[b] among 47,894 men in the health professionals cohort followed for 6 years.

	Quintile of intake[c]					
Carotenoid	1	2	3	4	5	*p* for trend
α-Carotene	1.0	1.05	1.09	1.07	1.09	0.77
β-Carotene	1.0	1.24	0.96	0.99	1.05	0.70
β-Cryptoxanthin	1.0	0.97	1.14	0.99	0.94	0.76
Lutein/zeaxanthin	1.0	1.01	1.01	0.96	1.10	0.34
Lycopene	1.0	0.90	0.94	0.89	0.79[d]	0.04
Mg/day	<2.3	2.3–3.4	3.4–4.6	4.6–6.5	>6.5	
Cases	180	147	154	145	147	
Person-years	52,183	52,903	52,990	52,756	52,277	

[a] Adjusted for age and energy intake.
[b] 773 non-stage A1 cases of prostate cancer.
[c] Intake for 1 year estimated with an 131-item "validated" semi-quantitative food frequency questionnaire.
[d] 95% confidence interval excludes 1.0.
Adapted from Giovannucci et al., 1995.

Table 3. Relative risks[a] of prostate cancer[b] among 47,894 men in the health professionals cohort followed for 6 years.

	Servings[c]				
Food	0	1–3/month	1/week	2–4/week	*p* for trend
Tomatoes					
RR	1.0	0.90	0.91	0.74[d]	0.03
Cases	148	161	300	155	
Tomato juice					
RR	1.0	1.02	0.85	1.15	0.67
Cases	378	207	65	77	
Tomato sauce					
RR	1.0	0.85	0.77[d]	0.66[d]	0.001
Cases	209	313	158	65	
Pizza					
RR	1.0	0.94	0.76	0.85	0.05
Cases	396	287	60	11	

[a] Adjusted for age and energy intake.
[b] 773 non-stage A1 cases of prostate cancer.
[c] "Validated" food frequency questionnaire included 46 vegetables, fruits, and related items.
[d] 95% confidence interval excludes 1.0.
Adapted from Giovannucci et al., 1995.

which had been calibrated against 9 days of dietary records in 109 volunteers. A total of 610 cases of prostate cancer were diagnosed over a 6.3 year followup. One explanation for the discrepant results from these two similar cohort studies is that, in the Dutch cohort, processed tomato products, such as tomato sauce and pizza, in which lycopene and similar biochemicals would be more bioavailable, were not included in the dietary questionnaire. In addition, the range of intake of raw tomatoes was not presented for the Dutch cohort and thus can not be compared with that in the U.S.

Like the three cohort studies discussed above, the twelve case-control studies that explored intake of tomatoes, tomato products, and/or lycopene and risk of prostate cancer did not produce consistent results (Table 1). Six showed reductions in risk of total or advanced prostate cancer of at least 20% with increasing intake of tomatoes, tomato products, or lycopene; four presented essentially null effects; one suggested an increase in risk of at least 20%; and one did not estimate relative risk. In only two studies were the estimates of reduced risk at the highest intake statistically significant;

Table 4. Summary of epidemiologic studies examining the relationship between circulating concentrations of lycopene and risk of prostate cancer.[a]

Authors	Study population	Cases		Exposure assessment		Exposure range	OR or RR (**Bold** = $p < 0.05$)	*P* for trend	Controlled factors
		No.	% advanced disease[b]	Timing	Plasma/serum				
Hsing et al., 1990	Maryland, USA	103	83%	Prosp	Serum	High vs. low quartiles	0.50	0.26	Age, race
Nomura et al., 1997	Hawaii, USA (Japanese-Americans)	142	72%	Prosp	Serum	High vs. low quartiles	1.10	0.86	Age, hour of examination, year and month of examination
Gann et al., 1999	USA (physicians)	578	45%	Prosp	Plasma	High vs. low quintiles	0.75 Advanced cases: **0.56**	0.12 **0.05**	Age, smoking status
Lu et al., 2001	USA (Hospital-based)	65	NK	Retro	Plasma	High vs. low quartiles	**0.17**	**0.01**	Age, race, family history of prostate cancer, education, pack-years of smoking, alcohol consumption, energy

[a] "NK" = "not known"; "mo" = "month"; wk = "week"

[b] "Advanced" disease is defined variously by researchers. Therefore, one specific definition could not be provided.

in one of these studies and in one additional study, the inverse trends reached statistical significance. Protective effects were reported more frequently with cooked tomato products than with raw tomatoes. Neither lycopene nor intake of tomato products was consistently a stronger predictor of reduced risk. However, the early databases for lycopene content of specific foods, on which many of the studies relied, have now been updated and improved (Tonucci et al., 1995). It is not possible to tell whether inverse relationships were generally stronger for advanced disease. Protective effects were most frequently observed among U.S. White men but were also reported in studies conducted in Greece and New Zealand. Comparing studies by absolute level of exposure might be informative. However, such an analysis is complicated by differences in the appropriateness and comprehensiveness of the dietary assessment instruments, metrics for summing tomato and tomato product consumption, and lycopene databases.

Table 5. Relative risks[a,b] of prostate cancer in a cohort of 6,860 Japanese-American men in Hawaii during 20 years of follow-up.[c]

	Serum levels, by quartile				
Carotenoid	1	2	3	4	*p* for trend
α-Carotene	1.0	1.5	1.7	1.2	0.99
β-Carotene	1.0	1.4	1.6	1.6	0.33
β-Cryptoxanthin	1.0	1.3	1.6	1.8	0.16
Lutein	1.0	0.5	1.0	1.0	0.66
Lycopene	1.0	1.0	1.0	1.1	0.86

[a] Nested case-control analysis matched on hour and date of exam, age at exam, and length of follow-up.
[b] None of the 95% confidence intervals excluded 1.0.
[c] Includes 142 prostate cancer cases and 142 controls.
Adapted from Nomura et al., 1997.

In addition to the epidemiologic studies of tomato and/or lycopene intake, four published studies have explored the relationship between blood lycopene levels and risk of prostate cancer (Table 4). Blood lycopene levels, unlike dietary estimates, are not dependent on cognitive ability and memory. In addition, they reflect absorption and metabolism as well as intake, are substantially more correlated with lycopene concentrations in prostate tissue than dietary measures, and thus may be an especially informative biomarker. One disadvantage of blood lycopene levels is that they are influenced by recent intake and may not reflect usual adult dietary patterns. Cross-sectional data from NHANES III indicate that blood lycopene levels decrease steadily with age (US Department of Health and Human Services, National Center for Health Statistics, 1996). However, when lycopene concentrations in blood samples collected 15 years apart from 260 volunteers were compared in a recent study, agreement was reasonable ($r \sim 0.35$) (Comstock et al., 2001).

In the earliest of the three nested case-control studies of blood lycopene concentrations and subsequent prostate cancer incidence, 103 men in a cohort of 25,802 Washington County, Maryland residents had developed prostate cancer (clinically apparent in 83% of the cases) during 13 years of followup (Hsing et al., 1990). Prostate cancer incidence was reduced by 50% (RR = 0.50, 95% CI = 0.20 – 1.29) among men in the highest lycopene quartile, relative to the lowest, and risk steadily decreased across quartiles although neither the risk estimate nor the trend reached statistical significance. However, in the second of these studies, involving 142 incident cases of prostate cancer (72% clinically apparent) diagnosed during 20 years of followup in a cohort of 6,860 Japanese men living in Hawaii, no relationship with prediagnostic blood lycopene levels was observed (Table 5) (Nomura et al., 1997). The third, and largest, of the nested case-control studies involved 578 prostate cancer cases, 45% with aggressive disease (percent clinically appar-

Table 6. Relative risks[a] of prostate cancer in 14,916 participants in the physicians health study during 13 years of follow-up.[c]

	Plasma levels, by quintile					
Carotenoid	1	2	3	4	5	*p* for trend
α-Carotene	1.0	1.11	0.97	1.14	0.77	0.09
β-Cryptoxanthin	1.0	0.85	0.87	0.88	0.80	0.29
Lutein	1.0	1.01	1.08	10.9	1.10	0.63
Lycopene						
ng/ml	≤261	262–353	354–442	443–580	≥581	
RRs, all subjects	1.0	0.89	0.90	0.87	0.75	0.12
RRs, placebo	1.0	0.72	0.70	0.58[b]	0.59[c]	0.01

[a] Nested case-control analysis matched on age at blood draw, smoking status, and length of followup.
[b] Includes 578 prostate cancer cases and 1,294 controls.
[c] 95% confidence interval excludes 1.0.
Adapted from Gann et al., 1999.

Table 7. Correlations[a] between plasma carotenoid levels and vegetable and fruit intake.[b]

	Plasma carotenoid				
Food group intake[c]	α-Carotene	β-Carotene	β-Cryptoxanthin	Lutein	Lycopene
Vegetables + fruits	0.54	0.43	0.44	0.39	−0.04
Vegetables	0.45	0.34	0.30	0.43	0.00
Fruits	0.53	0.45	0.54	0.21	−0.07
High-lycopene foods	0.11	0.19	0.27	0.17	0.20

[a] Pearson correlation coefficients.
[b] Includes 50 male and 49 female participants, aged 18–37 years, with a wide range in usual vegetable and fruit intake.
[c] Intake over the past year assessed with a self-administered 153-item food frequency questionnaire.
Adapted from Campbell et al., 1994.

ent not presented), who were diagnosed during 13 years of followup of 22,071 men enrolled in the Physicians' Health Study, a randomized, placebo-controlled prevention trial of aspirin and β-carotene (Gann et al., 1999). Prostate cancer incidence declined with increasing plasma lycopene levels (RR = 0.75, 95% CI = 0.54–1.06, for highest vs. lowest quintile; p for trend = 0.12) (Table 6). A more substantial, and statistically significant, reduction (RR = 0.56, 95% CI = 0.34–0.92) and trend (p = 0.05) were noted for aggressive disease. However, the protective effect was restricted to the placebo group, with no evidence for a trend among the men assigned to β-carotene. In neither this study nor that by Hsing and collaborators (1990) was there any evidence that circulating lycopene was preferentially reduced when blood was drawn close to diagnosis.

Thus, the three prospective studies of circulating lycopene levels and subsequent prostate cancer incidence are inconsistent, with two finding a 25–50% reduction in risk at the highest lycopene concentrations and no evidence of a protective effect in the third. The inconsistency corroborates the inconsistency noted among the three prospective and twelve retrospective studies of tomato and/or lycopene intake and prostate cancer risk. However, the two prospective studies that did report inverse relationships with blood lycopene levels, like most of the dietary studies that found inverse relationships, included predominantly White U.S. populations. The null study of blood lycopene levels was conducted among Japanese men living in Hawaii. While it is possible that a racial difference in genetic susceptibility exists, the most likely explanation is a difference in exposure. Median blood lycopene levels among controls were 320 ng/ml in the Maryland cohort (Hsing et al., 1990) and 388 ng/ml in the Physicians cohort (Gann et al., 1999), but only 134 ng/ml in the Hawaiian cohort. The stronger protective effects observed with tomato products than with raw tomatoes in the dietary studies also suggest a threshold effect since heat processing and addition of fat enhance the absorption of lycopene. Because it is difficult to compare lycopene intake in studies using different assessment instruments and databases, further studies of circulating lycopene levels will be best able to evaluate whether a minimum exposure must be attained to reduce prostate cancer risk.

It may be premature to assume the relationship between lycopene and prostate cancer is causal. Blood lycopene may simply be a biomarker of other phytochemicals in tomatoes, a healthy diet, and/or a prudent lifestyle. Several studies have shown a reasonably strong correlation between blood lycopene concentrations and lycopene intake, with correlations ranging from 0.16 to 0.47 (Michaud et al., 1998; Mayne et al., 1999; Freeman et al., 2000). Tomatoes, the major source of dietary lycopene, contain several nutrients and phytochemicals that are potentially protective. However, blood lycopene concentrations are generally not reliable indicators of total vegetable and fruit intake, one important aspect of a healthy diet. For example, in a cross-sectional study of 99 men and women with a wide range of usual vegetable and fruit intake, plasma levels of each of the major carotenoids, except lycopene, were predictive of vegetable and fruit intake (r = 0.39 – 0.54), but the correlation with blood lycopene was null (Table 7) (Campbell et al., 1994). Unlike the other carotenoids, blood lycopene concentrations are not elevated in non-smokers (Brady et al., 1996; Mayne et al., 1999). Nonetheless, there are other lifestyles related to prostate cancer etiology and detection that blood lycopene might reflect. For example, men with diets high in ketchup and pizza might, in addition to their unhealthful dietary behavior, ignore regular PSA screening and, ironically, have an decreased risk of prostate cancer because latent disease is not being detected (Kristal & Cohen, 2000). Alternatively, men with diets high in tomatoes and tomato sauce might be adhering to the Mediterranean diets believed to reduce cancer incidence because of their high content of plant-based foods, low content of red meat, and emphasis on olive oil (Trichopoulou et al., 2000). Finally, since lycopene is primarily transported in low density lipoproteins, and lycopene concentrations in blood are modulated by the relative concentrations of lipid

fractions (Brady et al., 1996; Michaud et al, 1998), blood lycopene may be a biomarker of lipid profiles that influence prostate carcinogenesis.

In summary, despite its appeal as a promising preventive strategy, the hypothesis that tomatoes and lycopene reduce the risk of prostate cancer is neither completely supported nor refuted by the epidemiologic research. The published literature has too many discrepancies to be persuasive; yet there is sufficient consistency, particularly in populations with high intake of bioavailable lycopene or high blood lycopene levels, to be provocative. Only a few studies focused on blood lycopene and prostate cancer have been published; additional ones should be informative, and the common metric will simplify comparison. If elevated blood lycopene continues to be predictive of reduced prostate cancer risk, then further examination of its determinants would be reasonable since it may be a biomarker of critical dietary patterns and/or lifestyles. Future studies of diet and prostate cancer should incorporate not only the updated lycopene databases but also more detailed assessment of tomato and tomato product intake. This will be challenging since so many mixed dishes, sauces, salsas, and condiments, with varying recipes and portion sizes, contain tomatoes. Direct measurement in prostate tissue of lycopene, and other carotenoids for comparison, should be incorporated into selected methodologic, metabolic, and epidemiologic studies. Finally, reliable intermediate markers for prostate carcinogenesis, when available and validated, will facilitate research on the protective promise of tomatoes and lycopene.

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